REPORT

Effect of Human T-Lymphotropic Virus Type I Infection on Non-Hodgkin's Lymphoma Incidence

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Background: **We previously reported from a case–control analysis that T-cell non-Hodgkin's lymphoma (NHL) was strongly associated with human T-lymphotropic virus type I (HTLV-I) infection in Jamaica and Trinidad and that the relative risk for HTLV-I infection was very high in younger patients.** ***Purpose:*** **The objective of this study was to estimate the age-specific incidence rates of NHL among HTLV-I–infected and HTLV-I–uninfected adults in Jamaica and Trinidad.** ***Methods:*** **Population rates of HTLV-I infection were calculated from available census reports and serosurvey data. Incidence rates for NHL were calculated from all incident cases in Jamaica during 1984-1987 (n = 135) and from all incident cases in Trinidad during 1986-1990 (n = 117). Using biopsy material, we determined whether the immunophenotype of the tumor cells was T cell, B cell, or other. NHL incidence rates were computed according to HTLV-I status, age, sex, and tumor phenotype for each country separately and for both countries combined by weighting to the relative population size of each country.** ***Results:*** **The age-standardized NHL incidence rate (mean ± SE) in Jamaica was 1.9 ± 0.2 per 100 000 person-years (PY). In Trinidad, the rate was 2.9 ± 0.4 per 100 000 PY. Overall, the incidence of NHL increased with age and was higher in males than in females. In the HTLV-I–infected population, the incidence of NHL was inversely related to age, and age-specific rates were higher in males than in females. The NHL incidence in those estimated to have acquired HTLV-I infection in childhood, however, showed no sex difference, and one in 1300 such carriers (95% confidence interval: one in 1100 to one in 1600) per annum were estimated to be at such risk. For T-cell NHL, as proxy for adult T-cell lymphoma/leukemia, incidence was highest in those patients infected with HTLV-I early in life (perinatally or via breast milk), with high, sustained risk from early adulthood in both sexes.** ***Conclusions:*** **While overall NHL incidence rates reveal that HTLV-I endemicity does not impose an exaggerated lymphoma burden on these populations, the risk for lymphoma among carriers who acquire infection early in life is dramatic and is consistent with the hypothesis that virus exposure early in life is most important for lymphomagenesis.** ***Implications:*** **Studies of HTLV-I carriers known to be infected in childhood may provide insight into markers intermediate in the lymphomagnetic process. Strategies to disrupt early-life transmission of HTLV-I, notably mother–infant transmission, may be critical in reducing the burden of lymphoreticular disease in these populations [J Natl Cancer Inst 87:1009-1014, 1995].**

Adult T-cell lymphoma/leukemia (ATL), a peripheral T-cell malignancy, is a clinicopathologic entity etiologically related to human T-lymphotropic virus type I (HTLV-I) infection (*1,2*). In HTLV-I–endemic areas, such as southern Japan and the Caribbean, ATL is a major constituent of the hemato-oncologic disease burden, falling under the rubric of non-Hodgkin's lymphoma (NHL). The lifetime risk for development of ATL after HTLV-I infection has been shown previously to be in the order of 3%-5% (*3-5*). Available data have led to the postulation of a multihit carcinogenesis model for the development of ATL after infection with HTLV-I, with events taking place over a 20- to 40-year period (*6,7*).

We have previously examined the relative odds of HTLV-I infection in NHL in a case–control setting in Jamaica and Trinidad. Patients with T-cell NHL (the best epidemiologic surrogate for ATL) were 18 times more likely in Jamaica and 63 times more likely in Trinidad to be HTLV-I infected compared with those with other NHL groups. There was also a significant inverse relationship between age at presentation with T-cell NHL and the likelihood of HTLV-I seropositivity (*8*), supporting the concept that infection with HTLV-I in some early critical period is necessary for HTLV-I–induced lymphomagenesis. However, the question of whether the effect of HTLV-I infection on NHL incidence also varies inversely with age was not explored.

The purpose of the present study was to compute NHL incidence rates grouped by HTLV-I exposure, age, sex, and phenotype by using data generated from registries of NHL in Jamaica and Trinidad. We can, therefore, make inferences about the absolute effects of HTLV-I in-

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fection on the development of NHL in these locales. Specifically, according to the distribution of HTLV-I infection in the general population, NHL incidence rates are instructive in epidemiologically elucidating the role of HTLV-I in the lymphomagenic process.

Subjects and Methods

Parallel registries of hematologic malignancies were established at the University Hospital of the West Indies in Jamaica in 1984 and at the two general hospitals in Trinidad in 1985. Criteria for patient selection included the following: 1) bona fide hematologic malignancy proved by histology, 2) residence at the site for at least the previous 5 years, and 3) age 15 years and older. Review and approval for the study were obtained from the Institutional Review Boards at the National Cancer Institute and in both sites (i.e., Jamaica and Trinidad) before the study was conducted. After giving written informed consent, all incident case subjects were enrolled and interviewed by trained study nurses. Continuing review of clinical charts yielded information about clinicopathologic, treatment, and follow-up variables. Data were edited and entered into analysis files on a mainframe computer.

Biologic specimens were collected from each case subject after giving written informed consent. Peripheral whole blood was collected for separation of serum and viable lymphocytes by the use of a density-gradient method. Biopsy material was fixed in formalin and paraffin embedded. Specimens were shipped to the National Institutes of Health for pathologic review and classified according to the National Cancer Institute Working Formulation (*9*). Serum was tested for antibodies to HTLV-I by the use of a whole-virus enzyme-linked immunosorbent assay (Cambridge-Biotech, Rockville, MD), and HTLV-I positivity was confirmed using a recombinant gp-21–enhanced immunoblot method (Cambridge-Biotech). All case subjects included in the study were assayed for HTLV-I antibodies. Presence of human T-lymphotropic virus type II (HTLV-II) was determined by using polymerase chain reaction (PCR) employing HTLV-II specific primers and probes. Tumor cell lineage was determined by immunophenotyping, which was performed on formalin-fixed and paraffin-embedded biopsy material or on circulating malignant cells by use of commercial monoclonal antibodies. The tumor cell phenotype was classified as T cell, B cell, or other (i.e., indeterminate or not available because of the difficulty in obtaining proper patient material during the aggressive, terminal stage of the disease).

Statistics

Incidence rates were standardized by the use of the World Standard population age structure (*10*). Age-specific NHL incidence rates were also compared. Standard errors for all standardized rates were computed from the variance by the use of conventional methods. To estimate the number of HTLV-I–exposed persons in the general population, we applied HTLV-I prevalence rates from population-based studies (*11,12*) in the two sites to population census figures (*13,14*). We assumed that HTLV-I population prevalence rates are stable over time. The number of HTLV-I–positive persons putatively infected in childhood was calculated according to the method described by Murphy et al. (*5*). Each 10-year cohort, stratified by sex, was projected back in time to its size when aged 0-9 years and 10-19 years by using historic census data. Known seroprevalence rates for HTLV-I at ages 0-9 years and 10-19 years were then applied to calculate the number of carriers infected early in life. Given that approximately 43% of the Trinidad population is of non-African race and that HTLV-I is found almost exclusively in people of African race there, we included only case subjects of African descent for the combined data. All rates represent the average annual incidence in the respective age group per 100 000 population; i.e., they have been averaged over the number of years included in the period of case registration (*10*). Rates were computed for Jamaica and Trinidad separately and were combined by weighting to the relative population size of each country.

Results

A total of 135 cases of NHL in Jamaica (1984-1987) and 117 cases of NHL in Trinidad (1986-1990) were registered. The overall NHL incidence rate, standardized to the hypothetical world population, in Jamaica was (means ± SE) 1.9 ± 0.2 per 100 000 person-years (PY) and 2.9 ± 0.4 per 100 000 PY in Trinidad. Rates were higher for males than for females in both sites: 2.0 ± 0.3 per 100 000 PY for males and 1.6 ± 0.2 per 100 000 PY for females in Jamaica and 3.5 ± 0.6 per 100 000 PY for males and 2.4 ± 0.5 per 100 000 PY for females in Trinidad. Age-specific rates for NHL (Fig. 1, A and B) increased with age for both males and females in both sites, with the highest rates occurring in those more than 60 years of age, 4.2 per 100 000 PY

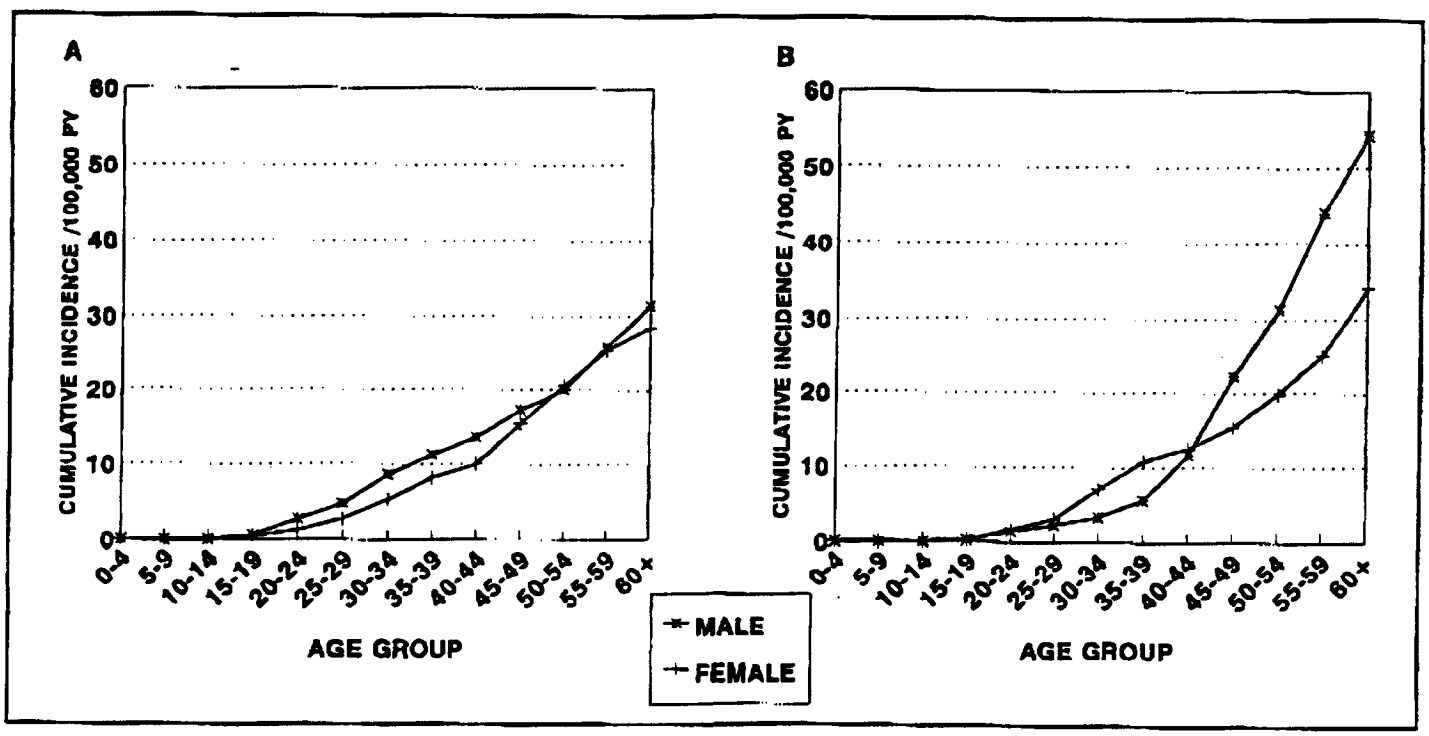

Fig. 1. Cumulative incidence of NHL by age and sex. A) Jamaica, 1984-1987. B) Trinidad, 1986-1990.

in Jamaica and 9.6 per 100 000 PY in Trinidad.

To better assess the relationship between NHL incidence, age, and HTLV-I status, we combined all case subjects of African race from Jamaica and all case subjects from Trinidad. Case subjects in the age group 15-19 years in both sites (n = 7), as well as case subjects of non-African race in Trinidad (n = 22), were excluded from further analysis. Total number of subjects excluded was 27, because two of the 22 non-African case subjects were also recorded in the age group 15-19 years. Jamaica's population in 1982 included 1 549 965 persons of both sexes aged 20 years or older of African race. The population of Trinidad and Tobago in 1980 included 603 149 persons of both sexes of African race; of these, 318 154 were 20 years old or older.

Table 1 shows age-specific rates grouped by HTLV-I status from both sites combined. Rates were highest for HTLV-I+ NHL; the rate in the age group 20-29 years was 35.5 per 100 000 PY and fell to 14.3 per 100 000 PY in the group aged 60 years or older. For those infections ascribed to childhood exposure, the rates were 66.5 per 100 000 PY in the group aged 20-29 years and 59.5 per 100 000 PY in the group aged 60 years or older. The corresponding rates among HTLV-I–negative subjects were 0.7 per 100 000 PY in the group aged 20-29 years, rising to 4.7 per 100 000 PY in the group aged 60 years or older. No evidence was found by PCR for presence of HTLV-II in the subjects selected by both registries.

Since an etiologic relationship has been established between HTLV-I and T-cell NHL in endemic areas, Table 2 examines average age-specific incidence rates for both sites grouped by immunophenotype and HTLV-I status. Rates were highest in the HTLV-I–positive T-cell NHL group and varied inversely with age, from 33.9 per 100 000 PY in the group aged 20-29 years to 7.3 per 100 000 PY in the group aged 60 years or older. The rate for B-cell NHL, of which only one case subject from each site was HTLV-I infected (and excluded from this analysis), was 0.2 per 100 000 PY in the group aged 20-29 years and increased directly with age to 1.4 per 100 000 PY in the group aged 60 years or older. Rates were intermediate in the HTLV-I–positive group, where tumor cell phenotype was indeterminate/not available (n = 79).

The T-cell NHL incidence was highest among those carriers whose infection was ascribed to childhood exposure and showed a pattern of sustained risk from early adulthood. Rates calculated in this way did not show the male excess of NHL reported for incidence rates based on all HTLV-I carriers. Fig. 2 graphically compares age-specific T-cell NHL incidence in HTLV-I carriers infected in childhood with the incidence of T-cell NHL in the total HTLV-I–infected population and overall NHL incidence in the HTLV-I–unexposed population.

Discussion

While HTLV-I is known to be etiologically related to ATL (*15*), the proportion of virus carriers at risk of developing this malignancy is not well defined. Since consensus for international comparison of ATL is only recently being developed (*16*), the current study examined all cases of NHL in two Caribbean countries with endemic HTLV-I infection. Overall, the incidence rates of NHL for both Jamaica

Table 1. NHL incidence in Jamaica and Trinidad by HTLV-I status (rates weighted by population size)

	Male*			Female*			Total No. of subjects*		
Age group, y	HTLV-I+†	HTLV-I+‡	HTLV-I–§	HTLV-I+†	HTLV-I+‡	HTLV-I–§	HTLV-I+†	HTLV-I+‡	HTLV-I–§
20-29	56.4 (11)	81.0 (11)	0.8 (7)	24.1 (8)	54.5 (8)	0.6 (6)	35.5 (19)	66.5 (19)	0.7 (13)
30-39	30.7 (7)	69.9 (7)	1.9 (11)	37.6 (16)	134.4 (16)	1.0 (6)	36.0 (23)	107.5 (23)	1.5 (17)
40-49	71.3 (14)	113.5 (14)	2.1 (9)	10.7 (5)	42.0 (5)	2.7 (11)	25.4 (19)	70.9 (19)	2.4 (20)
50-59	45.1 (9)	92.7 (9)	4.7 (17)	17.3 (10)	81.9 (10)	3.1 (10)	23.3 (19)	83.8 (19)	4.0 (27)
≥60	24.0 (10)	68.8 (10)	5.5 (26)	10.4 (10)	53.7 (10)	4.1 (22)	14.3 (20)	59.5 (20)	4.7 (48)
Total	39.9 (51)	88.7 (51)	2.0 (70)	15.7 (49)	66.1 (49)	1.6 (55)	24.1 (100)	75.2 (100)	2.2 (125)

*Rates per 100 000 person-years; case subjects and population of African descent. Absolute numbers of case subjects in parentheses.
†HTLV-I+ NHL incidence in total HTLV-I carriers in population.
‡HTLV-I+ NHL incidence in HTLV-I carriers infected in childhood.
§Seronegative NHL incidence in the HTLV-I–uninfected population.

Table 2. NHL incidence rates in Jamaica and Trinidad by phenotype and HTLV-I status (rates weighted by population size)*

Age, y	T cell, HTLV-I+*,†	T cell, HTLV-I+*,‡	T cell, HTLV-I–*	B cell, HTLV-I–*	Other HTLV-I+*,§	Other HTLV-I–*,§	Total No. of subjects*
20-29	33.9 (18)	64.5 (18)	0.2 (3)	0.2 (4)	1.6 (1)	0.3 (6)	1.6 (32)
30-39	26.4 (17)	75.9 (17)	0.6 (7)	0.4 (5)	9.6 (6)	0.4 (5)	3.3 (40)
40-49	17.1 (13)	51.6 (13)	0.8 (6)	0.8 (7)	8.3 (6)	0.8 (7)	4.4 (39)
50-59	16.3 (13)	58.2 (13)	1.4 (9)	1.2 (8)	7.1 (6)	1.4 (10)	6.0 (46)
≥60	7.3 (8)	23.2 (8)	1.4 (14)	1.4 (14)	8.7 (12)	1.9 (20)	5.9 (68)
Total	15.5 (69)	44.5 (69)	0.5 (39)	0.5 (38)	6.9 (31)	0.7 (48)	3.0 (225)

*Rates per 100 000 person-years; case subjects and population of African descent. Absolute numbers of case subjects in parentheses.
†HTLV-I+ T-cell NHL incidence found in total HTLV-I carriers in population.
‡HTLV-I+ T-cell NHL incidence in HTLV-I carriers infected in childhood.
§Other = indeterminate/not available phenotype.

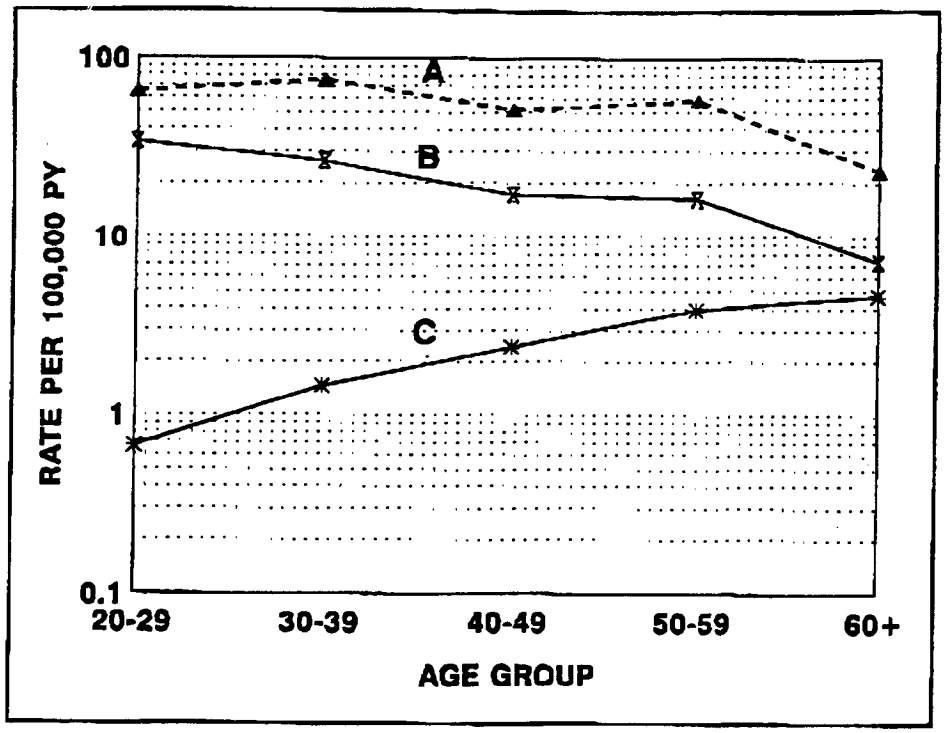

Fig. 2. Average incidence of NHL weighted by population size in Jamaica and Trinidad by age. Line A = T-cell NHL incidence in HTLV-I carriers infected during childhood. Line B = T-cell NHL incidence in total HTLV-I–infected population. Line C = overall NHL incidence in HTLV-I–uninfected population.

and Trinidad are comparatively low, being approximately one third of those for U.S. blacks of the corresponding time period (*17*), but higher than the rates in Kampala, Uganda (*18*), and similar to those in Japan (*19*). Thus, while HTLV-I is etiologically related to T-cell NHL, virus endemicity does not imply an exaggerated lymphoma or leukemia burden. It is possible that this discrepancy resulted from underascertainment of cases. In Jamaica, however, where cancer statistics have been registered since 1958, NHL incidence rates appear to be stable (*20*) so that, if underascertainment were a factor, this bias is persistent and unaffected by improved diagnostic approaches implicated as part of the reason for the rising worldwide incidence of NHL (*17*). The observation that there has not been a substantial rise in NHL incidence in Jamaica is noteworthy, and a study of the etiologic factors in this setting affords opportunities for furthering pathogenic insights.

As seen in most of the world, NHL incidence rates in this study population (Fig. 1) are directly proportional to age, with the highest rates occurring in the oldest age groups. By contrast, when incidence is calculated on the basis of the total subset of the population infected with HTLV-I, incidence is elevated within each age group, but the age trend is reversed, with the highest rates in the groups aged between 20 and 39 years (Table 1). Thus, the proportion of NHL cases that is HTLV-I related falls with age, even as the number of HTLV-I–infected persons in the population rises. This pattern mirrors relative risk estimates from a previously published case–control study in which the highest rates of HTLV-I infection were among T-cell NHL case subjects in the groups aged between 20 and 39 years in these countries (*8*).

The highest incidence rates and the most marked inverse relationship with age were found in HTLV-I–positive T-cell NHL cases, the disease category that defines ATL. Incidence rates were intermediate in the HTLV-I–positive group where phenotype was indeterminate or not available, representing cases of ATL whose aggressive clinical course made it impossible to collect appropriate materials before the patient's death. Conversely, the incidence of NHL in the HTLV-I–uninfected population was comparable to or lower than that observed in other developing countries (*19*) and rose gradually with age. Thus, at age 60 years or older, the incidence of T-cell NHL among all HTLV-I–positive subjects was similar to the incidence of NHL overall in the uninfected population.

A consistent feature of endemic HTLV-I infection is the age–prevalence relationship; the prevalence is low in persons younger than 20 years old but rises thereafter, with prevalence in females continuing to increase after age 40 years, while that in males tending to plateau at that age (*21*). While some of this pattern may be explained through a cohort effect (*22,23*), there is additional evidence for differentially greater male-to-female sexual transmission during adult life (*24*). This type of transmission has been shown to occur into the seventh decade (*25*).

Rates of all NHL in both Jamaica and Trinidad are higher in men than in women, with a male-to-female ratio of 1.15 (Fig. 1); this difference was statistically significant in Trinidad. The incidence of NHL among all persons with HTLV-I infection in the population was much higher in males than in females, with a male-to-female ratio of 2.5. This excess of lymphoma among male HTLV-I carriers compared with female carriers largely results from the much higher rate of HTLV-I infection among females which has been ascribed to more efficient male-to-female sexual transmission of HTLV-I. In the only comparable report from Japan (*26*), case ascertainment was achieved retrospectively, and total HTLV-I prevalence rates for the referent population were imputed from blood bank-screening data. The pattern of ATL incidence in the Japanese study (*26*) showed a male predominance with lowest rates in the oldest age group, identical to the pattern observed in this analysis. Rather than representing a deficit of female cases among carriers as suggested by the Japanese group, this pattern more likely represents the irrelevancy of adult acquired infection to subsequent ATL risk. In addition, in the Caribbean, the age of onset for HTLV-I–associated lymphoid malignancy for both males and females shows a unimodal distribution with a peak in the late forties (*27,28*). Thus, despite the increasing HTLV-I seroprevalence with age via sexual transmission, infection during adulthood does not seem to confer risk for ATL development. The alternative hypothesis is that infection with HTLV-I occurs in some

critical period early in life that facilitates HTLV-I lymphomagenesis.

The incidence rates of HTLV-I–positive NHL among those who acquired HTLV-I in childhood are higher at all ages than rates in the total HTLV-I–infected population, averaging 75.2/100 000 PY. The male-to-female rate ratio in this analysis is 1.34, which is more representative of the overall male-to-female ratio of 1.15 for all NHLs. This model of incidence, which is based on those subjects infected by perinatal or breast-milk transmission with a high risk of developing NHL at an early age suggests the overriding effect of early HTLV-I infection on subsequent risk for ATL.

We have estimated NHL incidence rates grouped on HTLV-I exposure in the populations of Jamaica and Trinidad. Since only those persons exposed to HTLV-I can be expected to develop an HTLV-I–related hemato-oncologic outcome, these rates give a more accurate estimate of the risk of lymphoma/leukemia in HTLV-I–endemic populations. Our data suggest that the most profound risk for the development of T-cell NHL, as a proxy for ATL, is infection with HTLV-I in some critical period in early childhood. When modeled in this way, the incidence of NHL is elevated from young adulthood and is sustained across the age spectrum, with little difference between males and females. In this context, a study of such carriers affords an opportunity to define additional oncogenic events that distinguish those who develop ATL from those who remain healthy. The relationship between HTLV-I infection and HTLV-I–associated malignancy, therefore, more closely follows the pattern seen in other human virus-induced malignancy models, such as hepatitis B/hepatocellular carcinoma (*29,30*), where approximately one in 200 hepatitis B surface antigen carriers subsequently develops hepatocellular cancer per annum, a lifetime risk exceeding 30%. A similarly high risk is observed in this study for HTLV-I–exposed individuals infected in childhood, where an estimated 1 in 1300 per annum childhood carriers develops ATL, a 3%-4.5% cumulative lifetime risk. Furthermore, these data show that the HTLV-I–infected population has completely typical risks of other types of lymphomas; i.e., HTLV-I does not appear to be a factor or cofactor in B-cell NHL.

The data also have public health implications. Studies of HTLV-I carriers known to be infected in childhood may reveal intermediate markers in the development of NHL/ATL. Even if eliminating HTLV-I infection proves unfeasible, interventions to reduce infection in early life, specifically mother-to-child transmission, will greatly reduce the hemato-oncologic disease burden of HTLV-I infection on endemic populations.

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Notes

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Have You Seen our Videotapes?

A videotape, *Finding Strength: A Look at the Pediatric Branch,* is available to health care professionals and families interested in learning more about programs and research protocols at the Branch. Also available are two videotapes for health care professionals working with HIV-infected children and their families: *Conducting an HIV Parent Support Group* and *I Need a Friend: Kids Talk About the AIDS Virus.*

If you plan to show the tape at a meeting of health professionals or other interested persons, we would be happy to arrange for a staff member to attend the showing and conduct a follow-up question and answer session. To schedule a presentation or order tapes, call Molly Matthews at (301) 951–1104.

Or Would You Like to Schedule a Speaker?

For patient referral or information, contact:

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